

**REMARKS/ARGUMENTS**

Reconsideration of this application is requested. Claims 12-41 are in the case

**I. INFORMATION DISCLOSURE STATEMENT**

The Examiner has crossed-out certain references from the PTO 1449, presumable because previously submitted copies were not in the USPTO file. For completeness, additional copies of the references crossed out are attached to the present response, together with a further copy of the PTO 1449. The Examiner is requested to initial the attached PTO 1449 and forward a copy of the initialed document to the undersigned with the next paper to issue in this case.

**II. THE 37 C.F.R. 1.75(c) OBJECTION**

Claims 9 and 10 are objected to under 37 C.F.R. 1.75(c) as allegedly improper. In response, and without conceding to the merit of this objection, claims 9 and 10 have been cancelled and the subject matter thereof re-presented as new claims 14-16. No new matter is entered. Withdrawal of this objection is now respectfully requested.

**III. THE 35 U.S.C. §112, SECOND PARAGRAPH, REJECTION**

Claims 8 and 11 stand rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite on lack of antecedent basis grounds. In response, claims 8 and 11 have been cancelled without prejudice and the subject matter thereof is presented in the new claims submitted herewith. Withdrawal of the outstanding 35 U.S.C. §112, second paragraph, rejection is accordingly respectfully requested.

**IV. THE 35 U.S.C. §101 REJECTION**

Claims 1-4, 12 and 13 stand rejected under 35 U.S.C. §101 as in "use" format. In response, claims 1-4 have been cancelled without prejudice and the subject matter thereof is re-presented in the claims submitted herewith. Claim 12 has been amended to recite a positive method step.

Withdrawal of the outstanding 35 U.S.C. §101 rejection is now believed to be in order. Such action is respectfully requested.

**V. THE OBVIOUSNESS REJECTION**

Claims 1-8 and 11-13 stand rejected under 35 U.S.C. §103(a) as allegedly unpatentable over the English translated copy of French Patent 2,687,070 in view of WO 94/29366 or WO 97/30073 and WO 97/39770. That rejection is respectfully traversed.

It is believed that the invention as now claimed is not suggested by the combined disclosures relied on by the Examiner. In this regard, the Examiner's attention is directed to the attached executed Declaration describing experiments which establish clear and unexpected advantage for the presently claimed method over that described in the closest prior art.

As stated in the specification at page 3, lines 4 to 6, the object of the present invention is to provide an alternative, and preferably safer, more reliable and/or more efficacious, anticoagulant effect during hemodialysis. This object is met by way of the invention as claimed , which provides a method of dialysis in which a low molecular

weight thrombin inhibitor is added to the dialysing solution prior to and/or during that dialysis (see also page 3, lines 24 to 27 of the instant specification).

FR '070 discloses a dialysis concentrate containing sodium heparinate, which is used to make up a dialysis solution for use in hemodialysis. The Examiner alleges that it would have been obvious for a skilled person to substitute a low molecular weight thrombin inhibitor, such a melagatran or inogatran, for sodium heparinate in the dialysis concentrate of FR '070 in the light of the disclosures of the three cited WO documents. This position is respectfully traversed.

As can be seen from the Material Safety Data Sheet attached as Exhibit B to the Fager declaration, sodium heparinate, as employed in the Examples of FR '070 (see page 3, fourth to last line to page 5, line 3 of the English translation thereof) has a molecular weight of *ca* 12,000. Even the low molecular weight heparins (which are not exemplified in the above-referenced passages in FR '070) have molecular weights in the region 2,500 to 8,000 (see page 3, line 3 of the translation). Dr. Fager notes that, by way of contrast, the term of art "low molecular weight thrombin inhibitor" will be understood by the person of ordinary skill to encompass compounds that inhibit thrombin and have a molecular weight below 2,000, more preferably below 1,000 (see page 7, lines 4 to 10 of the instant specification). Thus, the compounds referred to in the present claims are quite different in their character to those exemplified in FR '070. Moreover, in Dr. Fager's view, there is no motivation provided by any of the three cited WO documents to substitute a low molecular weight thrombin inhibitor for sodium heparinate as taught by FR '070.

This notwithstanding, the Fager declaration describes experiments which demonstrate unequivocally that, by providing a low molecular weight thrombin inhibitor, such as melagatran, to the dialysing solution prior to and/or during dialysis in accordance with in the presently-claimed method, not only can problems associated with standard prior art methodology (see page 2, lines 17 to page 3, line 2 of the instant specification) be solved, but also distinct and unexpected advantages are observed for such inhibitors when compared to the compounds and methodology described in FR '070. These experiments are described in detail in the Fager declaration.

Dr. Fager concludes that low molecular weight thrombin inhibitors, such as melagatran, may be delivered by way of a dialysing solution during hemodialysis and pass through dialysis filters. This is in complete contrast to both SH and Fragmin, where, despite what is stated in FR '070, the current results clearly show that delivery of those compounds by way of a dialysis solution prior to and/or during dialysis will not provide requisite concentrations of active substance in patient plasma to prevent clotting in blood lines and on the filter. In this way, a clear advantage is observed for the method claimed in the instant application that could not have been foreseen from the cited prior art.

In light of the above, it is clear that one of ordinary skill would not have been motivated to arrive at the presently claimed invention based on the combined disclosures of the cited prior art. Absent any such motivation, a *prima facie* case of obviousness has not been generated in this case. Withdrawal of the outstanding obviousness rejection is accordingly respectfully requested.

Allowance of the application is awaited.

FAGER, Gunnar .  
Appl. No. 10/098,625  
December 30, 2003

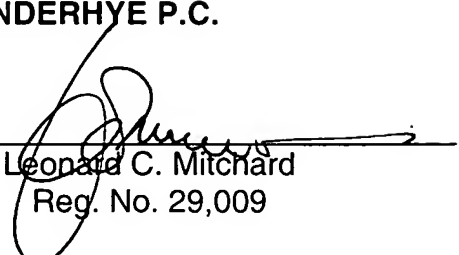


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Respectfully submitted,

**NIXON & VANDERHYE P.C.**

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Attachment: Executed Fager Declaration with Exhibits A and B  
PTO 1449; 0 468 231 A3; 0 526 877 A3; WO 96/24609); Chemical Abstracts, Vol. 129,  
Abstract No. 51430 (WO 98/23565 A2)